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The Structure and Total Synthesis of Futoenone, a Constituent of *Piper futokadzura* Sieb. et Zucc.[1)]

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A crystalline constituent, futoenone; $C_{20}H_{20}O_5$, mp 197°, was isolated from Piper futokadzura and proved to have the structure (I). The result of regenerating futoenone from the diacetate (Va) *via* the tosyl-phenol (X), providing an interesting example of Ar_1-6 participation, strongly supported the spiro-dienone structure of futoenone. The stereochemistry was also proposed by the data of NMR. The total synthesis of futoenone was accomplished.

Futoenone is one of the major components isolated from the leaves and stem of *Piper futokadzura* Sieb. et Zucc. (Piperaceae),[3)] which is widely distributed in the Pacific Coast of southern Japan.

Futoenone (I),[4)] $C_{20}H_{20}O_5$, mp 197°, shows in the infrared (IR) absorption bands at 1655, 1622, 1522 cm^{-1}, and in the ultraviolet (UV) maxima at 257, 285 mμ (ε 18900, 8800). Dihydrofutoenone (II), mp 173°, prepared by hydrogenation of futoenone using platinum oxide in ethanol, has the same chromophore showing the UV absorption at 259, 288 mμ (ε 12900, 3400). Reduction of futoenone with lithium aluminum hydride gave a mixture of epimeric alcohols (IIIa,b), mp 148—150°, [UV: 233, 288 mμ (ε 6000, 4500)]. Similarly, dihydrofutoenone (II) yielded corresponding alcohols (IVa, b), [UV: 233, 288 (ε 2900, 3300)], under the same reduction conditions. Since both mixture of the epimeric alcohols (IIIa, b and IVa, b) are oxidized with manganese dioxide to regenerate the starting ketones respectivley, and these alcohols show the characteristic absorption curve of a 3,4-methylenedioxyphenyl moiety,[5)] it is clear that futoenone has a piperonyl group and an α,β-unsaturated carbonyl group as the chromophores. The existence of piperonyl moiety is strongly supported by the mass spectrum shown in Fig. 1 revealing fragment peaks at *m/e* 163 and 135.

Treatment of futoenone with acetic anhydride in the presence of sulfuric acid or boron trifluoride furnished a mixture of epimeric diacetates (Va,b). The major product (Va), $C_{24}H_{26}O_8$, mp 111—112°, shows UV maxima at 232, 292 mμ (ε 9400, 7300) due to only an aromatic chromophore, and IR bands at 1755, 1710 cm^{-1} attributable to acetyl groups. Since the diacetates (Va, b) would be derived from futoenone without an elimination reaction, these derivatives must be key compounds for the structure elucidation of futoenone.

The 100 Mc nuclear magnetic resonance (NMR) spectrum of the diacetate (Va) was completely assigned as shown in Fig. 2. The chemical shifts for H_{7a}, H_{7b} and H_{10} (3.04, 2.67 and 2.97 ppm) are in accord with their being benzylic protons and the coupling constant between H_{7a} and H_{7b} (J=15.5 cps) indicates that these are geminal protons. The chemical shifts of

1) A portion of this work was reported as preliminary communications: A. Ogiso, M. Kurabayashi, H. Mishima, and M.C. Woods, *Tetrahedron Letters*, **1968**, 2003; M.C. Woods, I. Miura, A. Ogiso, M. Kurabayashi, and H. Mishima, *ibid.*, **1968**, 2009.
2) Location: *a) 2-58, Hiromachi 1-chome, Shinagawa-ku, Tokyo; b) Palo Alto, California, U.S.A.*
3) S. Takahashi and A. Ogiso, *Chem. Pharm. Bull.* (Tokyo), **18**, 100 (1970).
4) For the isolation, S. Takahashi, *Phytochemistry*, **8**, 321 (1969).
5) W.J. Gensler and C.M. Samour, *J. Org. Chem.*, **18**, 9 (1953).

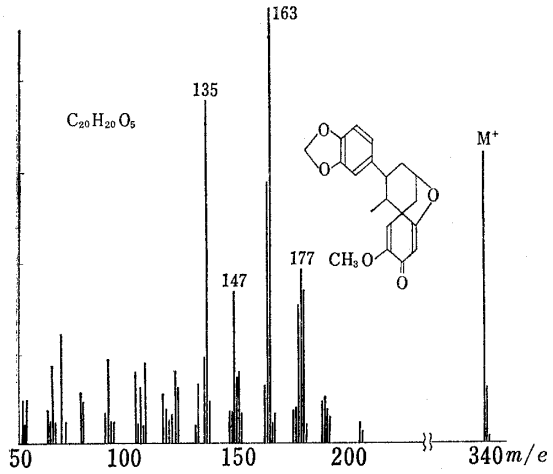


Fig. 1. Mass Spectrum of Futoenone

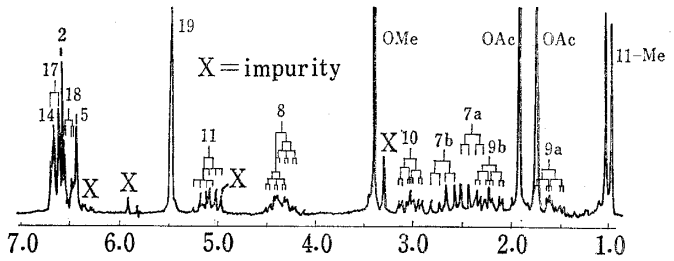
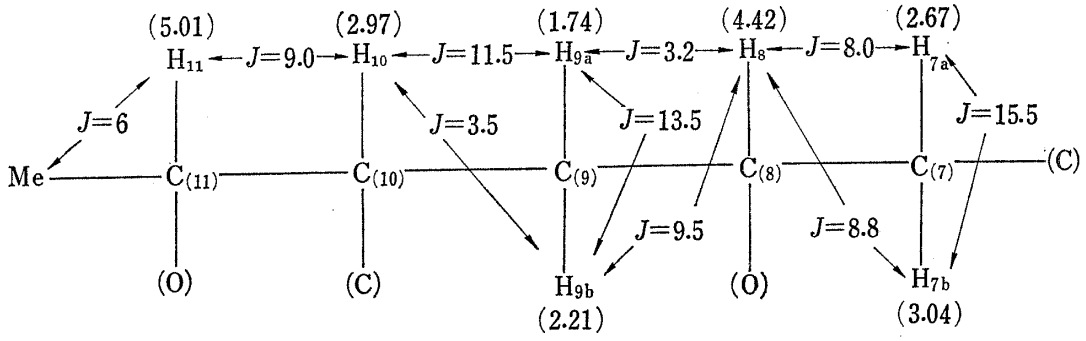


Fig. 2. NMR Spectrum of Diacetate (Va) in 87% C_6D_6–$CDCl_3$

H_8 and H_{11} present at lower fields (4.42, 5.01 ppm) points out that these are attached to carbons bearing oxygen. Thus, the partial structure of the diacetate (Va) was deduced as shown in structure A by the first-order analysis of the spectrum. The substituents of the aromatic rings could be assigned by the following data. The presence of a sharp singlet at 6.47 ppm and a broad singlet at 6.72 ppm suggests that these two protons (H_2, H_5) are *para* to each other. On irradiation of the signal due to methoxyl group at 3.69 ppm, a remarkable increase in height of the signal for H_5 took place but only a small change was shown on the signal due to H_2. The remaining three aromatic protons appeared as an ABC-system indicating 1,2,4-substitution in the second phenyl group. Since it has been shown by UV and IR that futoenone originally has a 3,4-methylenedioxyphenyl moiety, the arrangement of the substituents in the aromatic rings of the diacetate (Va) can be depicted as partial structures B and C.



A

Chart 1

In addition, decoupling experiments between the benzylic protons and the aromatic protons provided evidence that $C_{(7)}$ is connected to the aromatic ring C while $C_{(10)}$ to the 3,4-methylenedioxyphenyl group (B). From the above facts, deduction of the structure of the diacetate (Va) is straitforward except the position of the aromatic acetyl and the methoxyl groups.

Hydrolysis of the diacetate (Va) and benzylation of the resulting oily diol (VIa), followed by oxidation of the benzyl ether (VIIa) with chromiun trioxide in pyridine, afforded the methyl-

ketone (VIII). The structure of the methylketone (VIII) was confirmed from the absorption band at 1700 cm^{-1} in the IR and the singlet at 2.07 ppm attributable to three protons of the methyl group in the NMR. Moreover, the methylketone (VIII) derived from the diacetate (Va) is the key compound for structural determination of the isomeric diacetate (Vb). The isodiacetate (Vb), $C_{24}H_{26}O_8$, mp 124—125°, shows the same UV [232, 293 mμ (ε 9000, 7500)] but exhibits in the IR absorption at 1770 and 1725 cm^{-1}. The NMR of the isodiacetate (Vb) is almost superimposable with that of the diacetate (Va) except the doublet at 1.21 ppm due to a secondary methyl group. Hydrolysis of the isodiacetate (Vb) with alkali gave a crystalline isodiol (VIb), mp 125—126°, which was treated by the same procedure as for the diol (VIa): benzylation followed by oxidation, yielded the identical methylketone (VIII). The benzyl ether (VIIa) was treated with tosyl chloride in pyridine affording a mixture of futoenone and the tosylate (IX). The corresponding phenol (X), obtained by hydrogenolysis of the tosylate (IX), cyclized under basic conditions regenerating futoenone through Ar_1–6 participation[6] as shown in Chart 2. From the result of conversion of the diacetate (Va) into futoenone, the structure of the diacetate (Va) is confirmed unambiguously as well the structure of futoenone itself can be suggested. Namely, the conversion of futoenone into the diacetate (Va, b) can be considered as proceeding via a dienone–phenol type rearrangement involving fission of the $C_{(6)}$–$C_{(11)}$ bond followed by attack of an acetate anion. Interestingly, only one example of ring cleavage during an acid-catalyzed dienone–phenol rearrangement has been reported.[7]

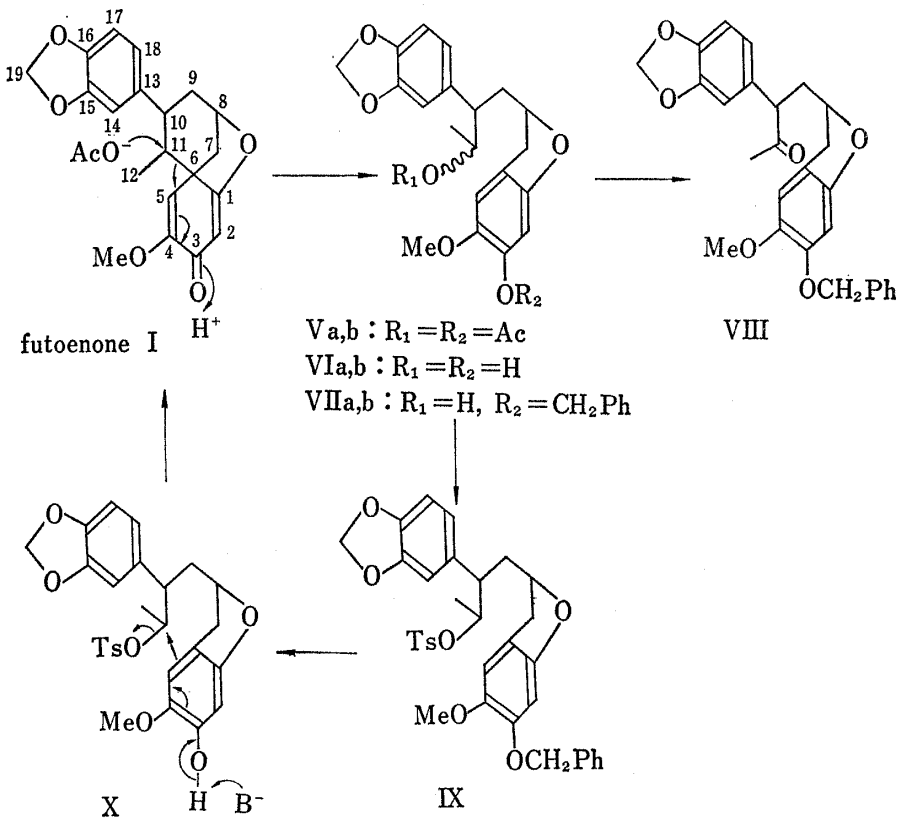


Chart 2

The dienone spirane structure of futoenone was strongly supported by following oxidative cleavage as shown in Chart 3. Permanganate–metaperiodate oxidation of futoenone followed by methylation of the acidic products gave an unsaturated δ-lactone (XI), mp 246°, and a γ-lactone (XII), mp 125—126°. The γ-lactone, $C_{17}H_{18}O_6$, showing IR absorption at 1795 cm^{-1}

6) S. Winstein, R. Heck, S. Lapporte, and R. Baird, *Experientia*, **12**, 138 (1956); S. Winstein and R. Baird, *J. Am. Chem. Soc.*, **79**, 756 (1957).
7) P.J. Kropp, *J. Am. Chem. Soc.*, **85**, 3280 (1963).

and NMR signals at 3.80 (-COOC$\underline{H}_3$), 0.90 (sec. -C$\underline{H}_3$) and 4.81 ppm (O-C$\underline{H}$), was proved to have structure XII. Also, the structure of the α,β-unsaturated δ-lactone (XI) was supported by the spectral data showing 1735, 1700, 1660 cm^{-1} in the IR and 3.87 (COOC$\underline{H}_3$), 5.38 (olefinic $\underline{H}$), 5.10 (O-C$\underline{H}$) and 0.83 ppm (sec. -C$\underline{H}_3$) in the NMR. Whereas, the demethyl derivative (XIII), prepared by treatment of futoenone with mineral acid, was oxidized with alkaline hydrogen peroxide and afforded, after methylation with diazomethane, the γ-lactone (XIV) (1765 cm^{-1}), mp 140°. Although the complete assignment of the 100 Mc spectrum of the γ-lactone (XIV) using double resonance techniques has been reported,[8] it is noteworthy to point out that the AB-quartet, consisting of a doublet at 2.54 ppm and a doublet at 2.86 ppm, due to a methylene protons supports the dienone spirane system in futoenone.

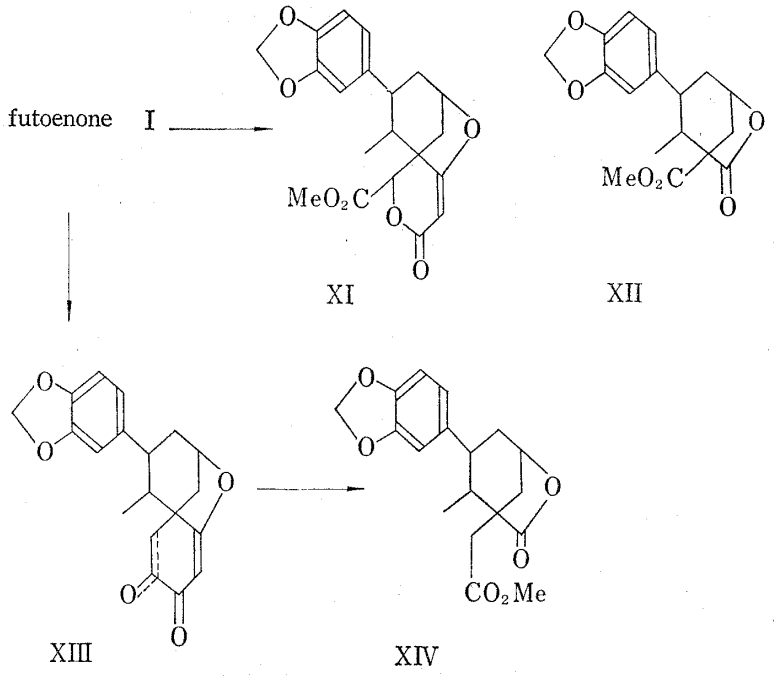


Chart 3

The NMR spectrum of futoenone shown in Fig. 3 is also assignable. The signals due to aromatic protons can be assigned to an ABC-pattern and must originate from the 3,4-methylenedioxyphenyl group. The partial structure of the dienone system F is deduced by the complete assignment of NMR of the epimeric alcohols (IIIa, b) as shown in Table I. The proton at 4.80 ppm (4.7 ppm for the isomer) attached to the carbinol is coupled with both olefinic protons at 4.97 ppm (5.12) and 4.64 ppm (4.71). Furthermore, the position of the methoxyl group can be determined by the fact that the methoxyl group is coupled with the olefinic proton at 4.64 ppm (4.71) in the NMR of the epimeric alcohols (IIIa, b), and in futoen-

Table I. NMR of Dienol Portion of Alcohols (IIIa,b)

	III_a	III_b		III_a	III_b
$J_{2,3}$	1.8	6.4	δ_3	4.80	*ca* 4.7
$J_{3,5}$	1.0	0.8	δ_5	4.64	4.71
$J_{5,OMe}$	*ca* 0.2	*ca* 0.2	δ_{OMe}	3.61	3.57
δ_2	4.97	5.12			

8) See reference 1).

one itself the olefinic proton at 5.49 ppm exhibits a nuclear Overhauser effect[9] when the methoxyl signal is irradiated.

Besides signals attributable to the 3,4-methylenedioxyphenyl moiety and the dienone part F, the NMR spectrum of futoenone contains a broad doublet of doublets centered at 5.01 ppm ($H_{8\alpha}$), a three proton doublet at 0.59 ppm due to a secondary methyl, and a complex pattern of signals in the 1.5 to 3.0 ppm region due to six protons. Strong irradiation of the secondary methyl signal converts the 11_α-proton signal into a doublet with 11.2 cps splitting, while decoupling of the broad doublet of doublets ($H_{8\alpha}$) causes the signals for $H_{7\beta}$ to change into doublet with splittings of 1.5 and 11.5 cps, and the multiplets due to $H_{9\beta}$ to appear as a doublet of doublets with splitting of 13.5, 5.0 and 1.5 cps, and in addition, sharpens the broad signals for $H_{9\alpha}$ at 1.70 ppm. In order to make an unambiguous assignment of all proton signals in the 1.0—3.0 ppm region, partial decoupling or spin perturbation technique was used as shown in Fig. 4. When the part of the multiplet due to $H_{10\beta}$ is irradiated, the signals due to $H_{9\alpha}$, $H_{9\beta}$ and $H_{11\alpha}$ show some sort of perturbation, while those due to $H_{7\alpha}$ and

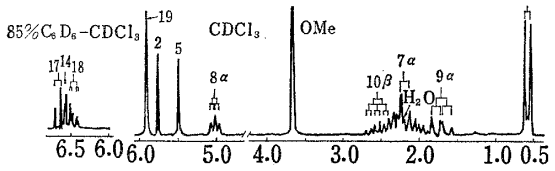


Fig. 3. NMR Spectrum of Futoenone (I)

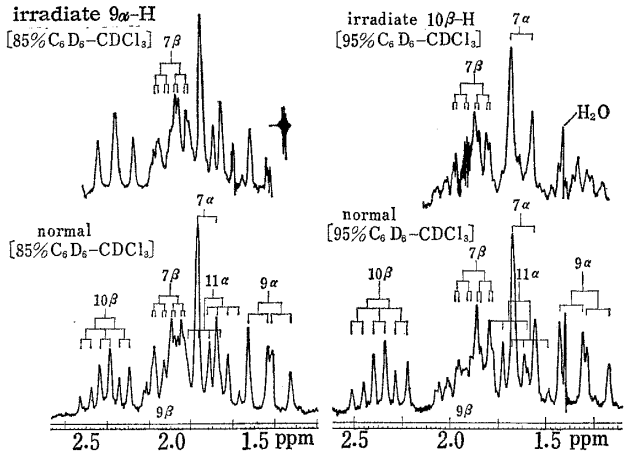
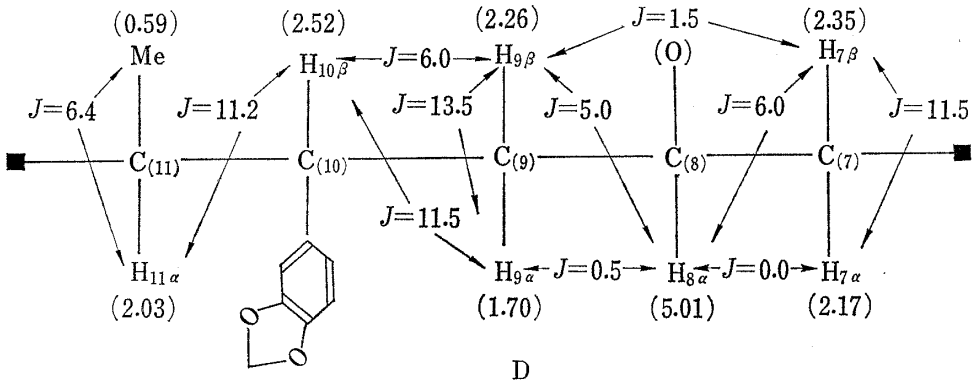


Fig. 4. NMDR, Spin-perturbation, of Futoenone (I)



D

E F

Chart 4

■ indictates a carbon bearing no proton

9) F.A.L. Anet and A.J.R. Bourn, *J. Am. Chem. Soc.*, **87**, 5250 (1965).

$H_{7\beta}$ remain unchanged. Similarly, irradiation of the 9α-proton signal causes perturbation of the signals due to $H_{9\beta}$ and $H_{10\beta}$ but does not effect the signals of $H_{7\alpha}$, $H_{7\beta}$ and $H_{11\alpha}$. From the NMR data mentioned above, it is clear that the partial structure D must be present in futoenone.

In addition to the fact that irradiation of the aromatic protons (H_{14} and H_{18}) increases in the height of signal due to $H_{10\beta}$, the chemical shift of the proton $H_{10\beta}$ indicates that 3,4-methylenedioxyphenyl group must be joined to $C_{(10)}$.

Since the partial structures D and F together account for nineteen carbons, all twenty hydrogens and all five oxygens in the futoenone molecule, $C_{(1)}$, $C_{(5)}$, $C_{(7)}$ and $C_{(11)}$ must all be linked to a spiro–carbon ($C_{(6)}$). Thus, the full structure of futoenone could be deduced as I.

The relative stereochemistry of futoenone can be determined by the following results. The stereochemistry of $C_{(12)}$ is necessarily defined by the bridged oxygen ring. $H_{10\beta}$, $H_{9\alpha}$ and $H_{10\beta}$, $H_{11\alpha}$ must be axial respectively because of the magnitudes of the coupling constants (both about 11.5 cps). Examination of a molecular model shows that the angles between $H_{7\alpha}$ and $H_{8\alpha}$, also $H_{8\alpha}$ and $H_{9\alpha}$, are close to 90° because of the oxygen bridge; this fact is in good agreement with the zero value of their coupling constants. Besides, it is noted that the secondary methyl signal appears at rather higher field (0.59 ppm) because of its orientation with respect to the dienone ring. An alternative possible stereochemistry in which the cyclohexane ring is constrained to a baot form, with quasi–equatorial methyl and aromatic groups is rejected for the following reasons. The coupling constant between $H_{7\alpha}$ and $H_{9\beta}$ (J=*ca.* 2 cps) is in accord with the coupling frequently observed across four bonds in a W–arrangement. The stereochemistry of the baot form has inverted configuration at $C_{(10)}$ and $C_{(11)}$ and interaction between the quasi–axial protons at $C_{(7)}$ and $C_{(10)}$ in the boat form would be expected to reduce the value of $J_{10,11}$ and $J_{9,10}$ below that of the observed values of 11.5 cps. In addition, the high–field shift of the signal due to the secondary methyl group can not be accounted for by such stereochemistry.

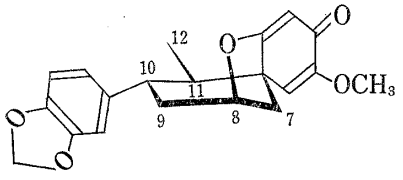


Chart 5

Finally, the synthesis of futoenone will be reported. Benzylscopoletin (XV)[10] was brominated in the presence of calcium carbonate and the crude bromide (XVI) was treated with aqueous sodium hydroxide to give 6-benzyloxy-5-methoxycoumalic acid (XVII), mp 209—210,° whose UV spectrum showed maxima at 277 and 317 mμ (ε 12600, 17500). On reduction with lithium aluminum hydride, the coumalic acid (XVII) was converted into 6-benzyloxy-2-hydroxymethyl-5-methoxybenzofuran (XVIII), mp 130—131° showing UV maxima at 249, 256, 295 and 300 mμ (ε 13900, 12900, 9200, 8800), which was oxidized with manganese dioxide to yield 6-benzyloxy-2-formyl-5-methoxybenzofuran (XIX), mp 100—101°. This oxidation to the aldehyde (XIX) caused a characteristic change in UV spectrum showing at 303 and 344 mμ (ε 11800, 18800). Condensation of the aldehyde (XIX) and piperonylacetone (XX) was effected by the Knoevenagel conditions using piperidine in benzene solution. Resulting yellow crystalline product, $C_{27}H_{22}O_6$, mp 170—171°, was found to be the desired compound because of the spectral date (see experimental section). Hydrogenation of the benzofurfurylidene piperonylacetone (XXI) afforded, after benzylation, an oily methylketone. Comparison of the oil with the methylketone (VIII) derived from natural product shows the materials are identical. Since the methylketone (VIII) was reduced with sodium borohydride to the alcohols (VIIa, b) and the alcohol (VIIa) could be converted into futoenone, the total synthesis of futoenone was accomplished.

10) E. Cingolani and A. Gaudiano, *Rend. Ist. Super. Sanita*, **19**, 1256 (1956); H.D. Braymer, M.R. Shetlar, and S.H. Wender, *Biochem. et Biophys. Acta*, **44**, 163 (1960).

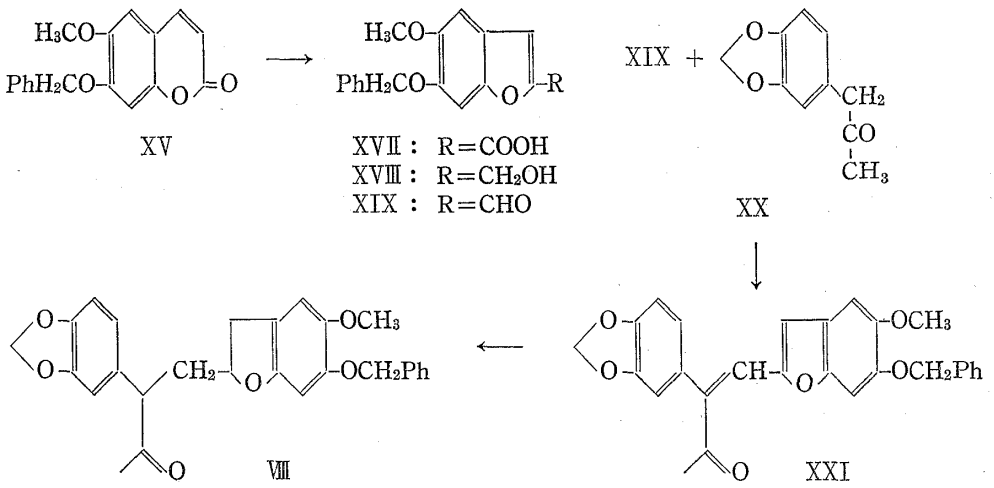


Chart 6

Experimental[11]

Hydrogenation of Futoenone[4]——A solution of 500 mg of futoenone in 100 ml of ethanol was hydrogenated using 50 mg of platinum oxide under atmospheric pressure at room temperature. One mole of hydrogen was taken up and the hydrogen absorption ceased. After filtration of the catalyst, the filtrate was evaporated to give 500 mg of dihydrofutoenone (II), which was recrystallized from *n*-hexane–acetone to give prisms, mp 174°. *Anal.* Calcd. for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 69.88; H, 6.56. UV λ_{max} mμ (ε): 259 (12900), 288 (3400). IR ν_{max} cm^{-1}: 1670, 1645. NMR ppm: 0.73 (3H, d), 3.58 (3H, s), 3.75 (1H, q), 4.95 (1H, m), 5.63 (1H, s), 5.95 (2H, s), aromatic (3H).

Lithium Aluminum Hydride Reduction of Futoenone——To a suspension of 500 mg of lithium aluminum hydride in 30 ml of dry tetrahydrofuran was added a solution of 1.0 g of futoenone in 20 ml of tetrahydrofuran. After stirring for 30 min at room temperature, the mixture was refluxed for 4 hr. Excess hydride was decomposed by addition of ethyl acetate and filtered. Evaporation of the solvent gave a white powder which was chromatographed on silica gel (10 g). Elution with benzene gave an epimeric mixture of alcohols (IIIa, b) which was recrystallized from *n*-hexane–acetone affording 600 mg of plates, mp 148—150°. *Anal.* Calcd. for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.30; H, 6.65. This substance showed two spots on thin-layer chromatography (TLC). UV λ_{max} mμ (ε): 233 (6000), 288 (4500). IR ν_{max} cm^{-1}: 3500.

Lithium Aluminum Hydride Reduction of Dihydrofutoenone (II)——Five hundred mg of the dihydrofutoenone (II) was reduced with 300 mg of lithium aluminum hydride in dry tetrahydrofuran. Working-up as in the same manner as the reduction of futoenone gave 200 mg of amorphous powder (IVa, b). UV λ_{max} mμ (ε): 233 (2900), 288 (3300).

Oxidation of Alcohols (IIIa, b)——A mixture of 300 mg of the alcohols (IIIa, b) and 1.6 g of manganese dioxide in 15 ml of chloroform was stirred vigorously for 2 hr at room temperature. After filtration, the chloroform solution was evaporated to give 250 mg of a crystalline residue. Recrystallization from *n*-hexane–acetone gave prisms, mp 195—197°, which was identical with futoenone in all respects; *i. e.*, TLC, IR, and showed no mixed melting point depression.

Oxidation of Dihydroalcohols (IVa, b)——The crude dihydroalcohols (IVa, b) (200 mg) was treated with 1.0 g of manganese dioxide in 10 ml of chloroform as in the procedure as the oxidation of alcohols (IIIa, b) to give 80 mg of crystals, mp 174°. These crystals were identical with dihydrofutoenone (II).

Acetylation of Futoenone——To a stirred solution of 3.0 g of futoenone in 50 ml of acetic anhydride was added 0.3 ml of concentrated sulfuric acid at 0°. After stirring for 4 hr at room temperature, the reaction mixture was poured into ice–water and extracted with ether. This extract was washed with aqueous sodium bicarbonate followed by water. Drying over sodium sulfate and evaporation of the solvent gave a crystalline mass, which was recrystallized from methanol to give 2.3 g of the diacetate (Va), mp 111—112°. *Anal.* Calcd. for $C_{24}H_{26}O_8$: C, 65.10; H, 6.22. Found: C, 65.10; H, 5.96. $[\alpha]_D^{23}$: −136.5° (c=2.06, $CHCl_3$). UV λ_{max} mμ (ε): 232 (9400), 292 (7300). IR ν_{max} cm^{-1}: 1755, 1710.

11) The melting points were determined in capillary tubes and uncorrected. The UV spectra were measured in 95% ethanol using a Beckman DK-2A spectrometer. IR spectra were determined in nujol, except where otherwise mentioned, on an Infracord spectrometer. The NMR spectra were determined with Varian A-60 and HA-100 spectrometer using tetramethylsilane as an internal reference in deuterochloroform.

From the mother liquors, the isodiacetate (Vb) was separated, which was recrystallized from methanol affording 250 mg of plates, mp 124—125°. *Anal.* Calcd. for $C_{24}H_{26}O_8$: C, 65.10; H, 6.22. Found: C, 65.04; H, 5.94. UV λ_{max} mμ (ε): 232 (9000), 293 (7500). IR ν_{max} cm^{-1}: 1770, 1725. NMR ppm: 1.21 (3H, d), 2.08 (3H, s), 2.27 (3H, s), 3.73 (3H, s), 5.95 (2H, s).

Saponification of Diacetate (Va)——To a solution of 1.2 g of the diacetate (Va) in 25 ml of ethanol was added a solution of 900 mg of potassium hydroxide in 2 ml of water and 12 ml of ethanol at room temperature. The solution was refluxed for 1.5 hr under nitrogen. The reaction mixture was poured into ice–water, washed with ether followed by acidification with concentrated hydrochloric acid under ice–cooling. The ether extract of the product was worked up as usual to give a quantitative yield of the oily diol (VIa). The oil showed single spot on TLC using silica gel.

Benzylation of Diol (VIa)——A solution of 900 mg of the diol (VIa) and 500 mg of benzyl chloride in 5 ml of dimethylformamide in the presence of 1.0 g of potassium carbonate was heated at 140° for 2.5 hr under vigorous stirring. The reaction mixture was poured into ice–water and extracted with ether. Drying the extract over sodium sulfate and evaporation of the solvent gave an oil which was chromatographed on silica gel (25 g). Elution with benzene containing 10% ethyl acetate gave 860 mg of a colorless oil which revealed one spot on TLC. IR ν_{max}^{liq} cm^{-1}: 3550. NMR ppm: 1.05 (3H, d), 3.78 (3H, s), 4.45 (1H, m), 5.08 (2H, s), 5.93 (2H, s).

Oxidation of Benzyl Ether (VIIa)——A solution of 760 mg of the benzyl ether (VIIa) in 4 ml of pyridine was added to Sarett's reagent prepared from 500 mg of chromium trioxide and 5 ml of pyridine. After standing overnight, the reaction mixture was diluted with ether and filtered. The filtrate was washed with water, dilute hydrochloric acid and water successively. The ether layer was dried over sodium sulfate and evaporated to give an oil which was chromatographed on silica gel (16 g). Elution with benzene gave 290 mg of crystals which was recrystallized from methanol followed by ether to yield needles, mp 105—106°. *Anal.* Calcd. for $C_{27}H_{26}O_6$: C, 72.63; H, 5.87. Found: C, 72.50; H, 5.53. IR ν_{max} cm^{-1}: 1700. NMR ppm: 2.07 (3H, s), 3.80 (3H, s), 4.45 (1H, m), 5.10 (2H, s), 5.97 (2H, s).

Saponification of Isodiacetate (Vb)——A solution of 310 mg of the isodiacetate in 20 ml of ethanol containing 250 mg of potassium hydroxide was refluxed for 1 hr under nitrogen. Working–up as the same manner as that of the diacetate (Va) gave the isodiol (VIb) which was recrystallized from ether gave 210 mg of plates, mp 125—126°. *Anal.* Calcd. for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 66.86; H, 6.28. IR IR ν_{max} cm^{-1}: 3550, 3330,

Benzylation of Isodiol (VIb)——Benzylation of 190 mg of the isodiol (VIb) was carried out by using 0.2 ml of benzyl chloride and 300 mg of potassium carbonate as in the procedure as for the diol (VIa). Purification of the product was effected by a preparative TLC using silica gel to give 180 mg of the isobenzyl ether (VIIb). NMR ppm: 1.28 (3H, d), 3.75 (3H, s), 4.7 (1H, m), 5.01 (2H, s), 5.87 (2H, s).

Oxidation of Isobenzyl Ether (VIIb)——Isobenzyl ether (120 mg) was oxidized with Sarett's reagent prepared from 100 mg of chromium trioxide and 1 ml of pyridine. The product purified by preparative TLC was identical with the methylketone (VIII) in all respects.

Tosylation of Benzyl Ether (VIIa)——A solution of 820 mg of the benzyl ether (VIIa) and 700 mg of *p*-toluenesulfonyl chloride in 8 ml of pyridine was allowed to stand overnight at room temperature. The solution was poured into ice–water and extracted with ether. The extract was washed with aqueous sodium bicarbonate, dilute hydrochloric acid and water. Drying over sodium sulfate and evaporation of the solvent gave a viscous oil. Elution with benzene on silica gel (20 g) give 570 mg of the tosylate (IX). NMR ppm: 1.11 (3H, d), 2.43 (3H, s), 3.83 (3H, s), 5.11 (2H, s), 5.98 (2H, s). Further elution with benzene–ethyl acetate (5:1) yielded a crystalline product whose TLC showed the formation of futoenone.

Hydrogenolysis of Tosylate (IX)——A solution of 550 mg of the tosylate (IX) in 25 ml of acetic acid was hydrogenated over 300 mg of 5% Pd–C. After removal of the catalyst, the solvent was evaporated. The residue was dissolved in ether and washed with aqueous sodium bicarbonate. The ether solution was dried and evaporated to give 300 mg of the oily phenol (X). IR ν_{max} cm^{-1}: 3500. NMR ppm: 1.13 (3H, d), 2.43 (3H, s), 3.80 (3H, s), 5.93 (2H, s).

Solvolysis of Phenol (X)——A solution of 230 mg of the phenol (X) eluted into a column of basic alumina (10 g). The column was eluted slowly with ethyl acetate to give an oil which was separated to give 30 mg of the oily starting material and 60 mg of crystals. The crystalline product was recrystallized from *n*-hexane–acetone to afford prisms, mp 196—197° which was identical with futoenone in all respects; *i. e.*, TLC, UV, IR and mixed melting point.

Lemieux Oxidation of Futoenone——To a solution of 1.35 g of futoenone in 200 ml of purified dioxane containing 10 ml of aqueous solution of sodium carbonate (350 mg) was added a solution of 8.5 g of sodium metaperiodate and 350 mg of potassium permanganate in 80 ml of water at room temperature. The reaction mixture was stirred vigorously for three days keeping the permanganate color during the period by addition of a small amount of potassium permanganate. After addition of a saturated aqueous solution of sodium bisulfite until a clear solution was given, the reaction mixture was concentrated to remove almost all of dioxane. The residue was extracted with chloroform and the extract was shaken with 5% aqueous sodium carbonate. From the neutral fraction, 350 mg of the starting material was recovered. The aqueous layer

was acidified with concentrated hydrochloric acid and extracted with chloroform to give 650 mg of a carboxylic acid mixture, which was methylated with diazomethane followed by column chromatography on silica gel (20 g). Elution with chloroform gave the γ-lactone (XII) which was recrystallized from ether to obtain 100 mg of prisms, mp 125—126°. *Anal.* Calcd. for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 64.18; H, 5.67. IR ν_{max} cm^{-1}: 1795, 1700. NMR ppm: 0.90 (3H, d), 3.80 (3H, s), 4.81 (1H, m).

Further elution with chloroform gave the unsaturated δ-lactone (XI), which was recrystallized from *n*-hexane–acetone to give 150 mg of plates, mp 246°. *Anal.* Calcd. for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41. Found: C, 64.61; H, 5.40. IR ν_{max} cm^{-1}: 1735, 1700, 1660. UV λ_{max} mμ (ε): 238 (17100), 287 (4400). NMR ppm: 0.83 (3H, d), 3.87 (3H, s), 4.81 (1H, s), 5.10 (1H, m), 5.38 (1H, s), 5.93 (2H, s).

Acid Treatment of Futoenone——A suspension of 1.0 g of futoenone in 150 ml of 30 w/w% sulfuric acid was heated on a steam-bath with stirring for 1.5 hr. The reaction mixture was diluted with water and resulting precipitate was collected by filtration. The precipitate was chromatographed on silica-gel (15 g) and elution with ethyl acetate gave 400 mg of the demethylfutoenone (XIII), which was recrystallized from ethanol to afford colorless plates, mp 190—194°. *Anal.* Calcd. for $C_{19}H_{18}O_5$: C, 69.92; H, 5.56. Found: C, 69.78; H, 5.50. UV λ_{max} mμ (ε): 263 (14400), 288 (13200). IR ν_{max} cm^{-1}: 3450 (weak), 1667.

Hydrogen Peroxide Oxidation of Demethylfutoenone (XIII)——To a suspension of 270 mg of demethylfutoenone in 14 ml of water containing 1.0 g of potassium hydroxide was added 6 ml of 30% hydrogen peroxide under ice-cooling. After being stirred for 24 hr at room temperature, the reaction mixture was diluted with water and washed with ether. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether. Evaporation of the solvent gave 240 mg of an amorphous solid which was methylated with diazomethane. Column chromatography on silica gel (10 g) gave 150 mg of the γ-lactone (XIV) in benzene eluates, which was recrystallized from ether to yield prisms, mp 140°. *Anal.* Calcd. for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 64.94; H, 5.96. IR $_{max}$ cm^{-1}: 1765, 1730. NMR ppm: 0.78: (3H, d), 2.54 (1H, d), 2.86 (1H, d), 3.67 (3H, s), 4.85 (1H, m), 5.90 (2H, s).

6-Benzyloxy-5-methoxycoumalic Acid (XVII)——To a stirred mixture of 5.6 g of benzylscopoletin and 5.0 g of anhydrous calcium carbonate in 50 ml of chloroform was added dropwise a solution of 3.4 g of bromine in 20 ml of chloroform under ice-cooling. Excess bromine was decomposed by addition of 30 ml of 20% aqueous sodium sulfite followed by stirring for 30 min at room temperature. The separated chloroform layer was washed with water and evaporated to give a pale yellow crystalline residue. The residue was triturated with ether and filtered to furnish 6.0 g of the bromide (XVI).

A suspension of 6.0 g of the crude bromide (XVI) in 500 ml of 10% potassium hydroxide was refluxed for 2 hr under stirring. After cooling, the resulting clear solution was acidified with concentrated hydrochloric acid to precipitate crystals. The collected crystals were washed with water and recrystallized from ethanol to give 4.0 g of the coumalic acid (XVII), mp 209—210°. *Anal.* Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.29; H, 4.91. UV λ_{max} mμ (ε): 277 (12600), 317 (17500). IR ν_{max} cm^{-1}: 2700, 1680, 1620, 1550.

6-Benzyloxy-2-hydroxymethyl-5-methoxybenzofuran (XVIII)——To a suspension of 2.0 g of lithium aluminum hydride in 100 ml of tetrahydrofuran was added a solution of 4.6 g of 6-benzyloxy-5-methoxycoumalic acid (XVII) in 50 ml of tetrahydrofuran under ice-cooling. The mixture was stirred for 3 hr at room temperature. After careful addition of ethyl acetate and water, the mixture was diluted further with ethyl acetate, and the organic phase separated and washed with dilute sulfuric acid and water. Drying over sodium sulfate and evaporation of the solvent gave hydroxymethylbenzofuran (XVIII) which was recrystallized from *n*-hexane–acetone to give 3.6 g of prisms, mp 130—131°. *Anal.* Calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.87; H, 5.86. UV λ_{max} mμ (ε): 249 (13900), 256 (12900), 295 (9200), 300 shoulder (8800). IR ν_{max} cm^{-1}: 3600, 1625, 1490.

6-Benzyloxy-2-formyl-5-methoxybenzofuran (XIX)——A solution of 7.8 g of the hydroxymethylbenzofuran (XVIII) in 150 ml of chloroform was treated with 50 g of manganese dioxide for 3 hr at room temperature. The reaction mixture was filtered and the filtrate was evaporated to dryness to give 7.2 g of the aldehyde (XIX) which was recrystallized from methanol to yield prisms, mp 100—101°. *Anal.* Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.08; H, 4.99. UV λ_{max} mμ (ε): 303 (11800), 344 (18800). IR ν_{max} cm^{-1}: 1665, 1605, 1540, 1480.

Condensation of Aldehyde (XIX) with Piperonylacetone (XX)——A solution of 5.4 g of the aldehyde (XIX) and 3.5 g of piperonylacetone (XX) in 50 ml of benzene containing 0.2 ml of piperidine was refluxed azeotropically for 12 hr. The reaction mixture was washed with dilute hydrochloric acid and evaporated to give a red oil. Column chromatography of the oil on silica gel (80 g) gave the benzofurfurylidene piperonylacetone (XXI) in the benzene eluates. Recrystallization from ethanol gave 2.5 g of yellow plates, mp 170—171°. *Anal.* Calcd. for $C_{27}H_{22}O_6$: C, 73.29; H, 5.44. Found: C, 72.93; H, 5.30. UV λ_{max} mμ (ε): 285 (5800), 382 (21800). IR ν_{max} cm^{-1}: 1665, 1658, 1610, 1540, 1500, 1485. NMR ppm: 2.28 (3H, s), 3.83 (3H, s), 5.13 (2H, s), 6.02 (2H, s), 6.11 (1H, broad s).

Hydrogenation of Benzofurfurylidene Piperonylacetone (XXI)——A solution of 1.0 g of the benzofurfurylidene piperonylacetone in 15 ml of acetic acid was shaken in a hydrogen atmosphere in the presence of 50 mg of platinum oxide as catalyst. After filtration, the solution was evaporated to give an oil which was treated

with benzyl chloride using potassium carbonate in dimethylformamide to give a crude benzyl ether (XXII). Column chromatography on silica gel gave 700 mg of an oily product. TLC of the oil showed single spot and the IR spectrum taken in chloroform (1715, 1610, 1500, 1480 cm^{-1}) was superimposable with that of the methylketone (VIII) derived from natural futoenone. NMR ppm: 2.06 (3H, s), 3.80 (3H, s), 4.5 (1H, m), 5.10 (2H, s), 5.98 (2H, s).

Sodium Borohydride Reduction of Methylketone (VIII)——A solution of 200 mg of the methylketone (VIII) and 100 mg of sodium borohydride in 10 ml of ethanol was allowed to stand overnight. Excess borohydride was decomposed by addition of acetic acid, the solution was evaporated and extracted with ether. The ether extract was dried over sodium sulfate and evaporated to give an oil. The spectrum data showed that the product was an epimeric mixture of the alcohols (VIIa and VIIb). NMR ppm: 1.05 (d), 3.78 (s), 4.45 (m), 5.08 (s), 5.93 (s), 1.26 (d), 5.87 (s).

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